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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,734	08/25/2006	Jerome Bernard	2121-0191PUS1	1220

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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
JIANG, DONG	

ART UNIT	PAPER NUMBER
1646	

NOTIFICATION DATE	DELIVERY MODE
04/24/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/590,734	BERNARD ET AL.	
	Examiner	Art Unit	
	DONG JIANG	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *1-3,16-26,31-36 and 38-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-7* is/are rejected.

7)☒ Claim(s) *8-15,27-30 and 37* is/are objected to.

8)☒ Claim(s) *1-43* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/30/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicant's election with traverse of Group III invention, claims 4-15, 27-30 and 37, filed on 28 November 2008 is acknowledged. The traversal is on the ground(s): 1) that the present application is the first description of the epitopes of IL-15, and these epitopes are novel and inventive, at least for that reason, unity of invention should have been acknowledged; 2) that the muteins in Groups III and IV derive from said epitopes, and share at least this corresponding special technical feature(s) which are based on the identification of said IL-15 epitopes, and that it is not understood how the alleged fact that products would be physically and/or functionally distinct chemical entities would provide any legal basis to an objection on the ground of lack of unity of invention in the sense of Rule 13.1 PCT, and how the alleged assumption that a certain subject-matter would not correspond to the main Invention would provide any legal basis to an objection on the ground of lack of unity of invention in the sense of Rule 13.1 PCT; and 3) that if the reasoning of the current Office Action were to be followed, it should then be recognized that groups III and IV are linked by a single inventive concept under Rule 13.1 PCT, groups V and VI relate to the nucleic acids coding for the muteins of Group III-IV, and therefore share a corresponding special technical feature in the sense of Rule 13.1 PCT, groups VII, VIII and IX relate to some applications that can be made of the muteins of the invention, and that therefore, the subject-matter of groups VII, VIII and IX share a special technical feature in the sense of Rule 13.1 PCT with Group III-IV, as a consequence, unity of invention of Groups III - IX should be acknowledged. This is not found persuasive for the following reasons.

With respect to point 1), as addressed in the last Office Action, the main invention (claim 1, for example, as written) is not novel. As such, the technical feature of the peptide is not special, and the groups do not share a special technical feature, and are not so linked by a single inventive concept under PCT Rule 13.1. With respect to point 2), group III is drawn to an IL-15 mutein that is an IL-15 agonist, whereas group IV is drawn to an IL-15 mutein that is an IL-15 antagonist. Thus, the products in these two groups share neither structure nor function, therefore, there is no special technical feature within the meaning of PCT Rule 13.2 so as to form a single general inventive concept. With respect to point 3), once again, as addressed in the last Office

Action and above, the *main invention* is not novel and does not makes a contribution over the prior art in view of Grabstein et al. (US5,552,303). Thus, the technical feature of the peptide is not special, and the groups do not share a special technical feature, and are not so linked by a single inventive concept under PCT Rule 13.1.

However, upon further consideration, the examiner decided to withdraw the restriction requirement between Groups III and IV, and imposed a species election between an IL-15 agonist (the original Group III) and an IL-15 antagonist (the original Group IV).

Currently, claims 1-43 are pending, and claims 4-15, 27-30 and 37 are under consideration as they read on the elected invention (species, an IL-15 agonist). Claims 1-3, 16-26, 31-36 and 38-43 are withdrawn from further consideration as being drawn to a non-elected invention/species.

Formal Matters:

Information Disclosure Statement

Applicant's IDS submitted on 1/30/07 is acknowledged and has been considered. A signed copy is attached hereto.

Note, it is indicated on IDS that there are three pages, however, only pages 1-2 are present on the record. Clarification is required in response to the instant Office Action.

Priority acknowledgement

This application is a national stage entry (371) of PCT/EP2005/002367 with the international filing date of 2/10/05, which is acknowledged.

Drawings & sequences

The drawings/figures are objected to for the following reasons: in "Figure 1A (end)", it is indicated that the sequence shown has 114 amino acids, and is SEQ ID NO:2. However, SEQ ID NO:2 on the sequence listing differs from that in the figure as it has 162 amino acids. Additionally, in the specification, under "Description of the figures" on page 5, the figure legend for Figure 1A states "the sequence of the human mature IL-15 protein (SEQ ID NO:2)" (line 13),

which is also incorrect. Further, in Figure 1B, "peptide1:", the number 45 is misplaced on top of L44 (instead of L45).

Appropriate correction is required.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (page 10, line 3, and page 20, line 26, for example). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claims

Claims 8-15, 27-30 and 37 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claims 4-7 are objected to for the following informalities, and appropriate correction is required for each item:

The claims recite "IL-15 mutein", the following is suggested: "An IL-15 mutein".

Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is indefinite for the recitation "at least one ... addition with in the region spanning ..." because it is unclear as to how many additions can be added, i.e., what is the upper limitation of numbers of amino acids for the addition to take place. The claim is further indefinite for the recitation "an affinity for binding … not significantly different from …" because the term "not

significantly different" is a relative term. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear how much change (higher or lower) in the binding affinity would be considered "not significantly different" or "significantly different". The metes and bounds of the claim, therefore, cannot be determined. Claim 5 is similarly indefinite.

The remaining claims are included in this rejection because they are dependent from the specifically mentioned claims without resolving the indefiniteness issue belonging thereto.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to an IL-15 mutein having one substitution at position L45, Q48, V49, S51 or L52 within the region spanning residues 44-52 (according to Figure 1A), *or* having one substitution within the region spanning residues 64-69, wherein the IL-15 mutein retains the binding affinity for IL-15Rα, does not reasonably provide enablement for claims to an IL-15 mutein having *at least one substitution, deletion or addition* within the region spanning residues 44-52, *and* within the region spanning residues 64-69. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claims 4 and 5 are directed to an IL-15 mutein having at least one substitution, deletion or addition within the region spanning residues 44-52, and/or within the region spanning residues 64-69, wherein the IL-15 mutein retains the binding affinity for IL-15Rα. However, the

specification merely teaches the IL-15 muteins with a single amino acid substitution within the region spanning residues 44-52, or residues 64-69. The specification does not teach any other form of sequence modification such as deletion and addition, nor amino acid substitutions in both regions. According to the specification, the two regions spanning residues 44-52 and residues 64-69 are directly involved in the binding to IL-15Rα (page 32, lines 9-10, for example). For example, mutations at three positions (E46, V49 and I50) within peptide 1 had profound effects on the affinity of IL-15 (page 27, lines 10-11). Thus, deletion of the regions would most likely abolish the binding property of IL-15 to IL-15Rα. Similarly, addition of undefined number of amino acids in these two regions would likely to disrupt the binding regions. Further, since these two regions are important for the receptor binding, mutations in both areas at once would be likely to unpredictable impact on the receptor binding of the molecule. Furthermore, although the specification discloses that the two regions spanning residues 44-52 and residues 64-69 are involved in the binding to IL-15Rα, the experimental results also show that the IL-15 muteins generated by single amino acid substitution within the region spanning residues 44-52 are potential IL-15 agonists (Figure 4A and B, and Figure 5A and B, and page 12, lines 14-15, for example), whereas the IL-15 muteins generated by single amino acid substitution within the region spanning residues 64-69 are potential IL-15 antagonists (Figure 4C and Figure 5C, page 13, lines 28-29, and page 35, lines 10-13, for example). Given this mutually exclusive nature (agonist vs. antagonist) of the IL-15 muteins generated from the two regions separately, it would be unpredictable that an IL-15 muteins with amino acid substitutions from both regions would maintain the desired the property.

Furthermore, within the region spanning residues 44-52, the specification teaches that mutations at three positions (E46, V49 and I50) within peptide 1 had *profound* effects on the affinity of IL-15 (page 27, lines 10-11), and they almost diminished the receptor binding of the muteins (Figures 4A and B). Therefore, only those muteins having one substitution at position L45, Q48, V49, S51 or L52 within the region spanning residues 44-52, but not "an IL-15 mutein having at least one substitution within the region spanning residues 44-52", are enabled.

Due to the large quantity of experimentation necessary to generate a huge number of muteins recited in the claims ("at least one", "substitution, deletion, or addition", and "and/or")

and possibly screen same for activity, the absence of working examples directed to same (other than the single amino acid substitutions in one of the two areas), and the presence of some muteins with a single amino acid substitution and diminished receptor binding activity, the complex and unpredictable nature of the invention, and the breadth of the claims which embraces a broad class of structural variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Prior Art:

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Grabstein et al. (US5,552,303, 9/3/96) discloses a novel T-cell growth factor, referred to as epithelium-derived T-cell factor (ETF), which amino acid sequence of SEQ ID NO:2 is 96.3% identical to the present SEQ ID NO:2 (human IL-15). It is further noted that Grabstein's ETF of SEQ ID NO:2 comprises an amino acid substitution at position 52 (and positions 57 and 58) of the mature hIL-15 according to the present "Figure 1A (end)" (see computer printout of the search results).

Conclusion:

No claim is allowed.

Advisory Information:

Any inquiry concerning this communication should be directed to Examiner Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Dong Jiang/
Primary Examiner, Art Unit 1646
2/28/09